# Clinical Trial Update: Needs and Progress

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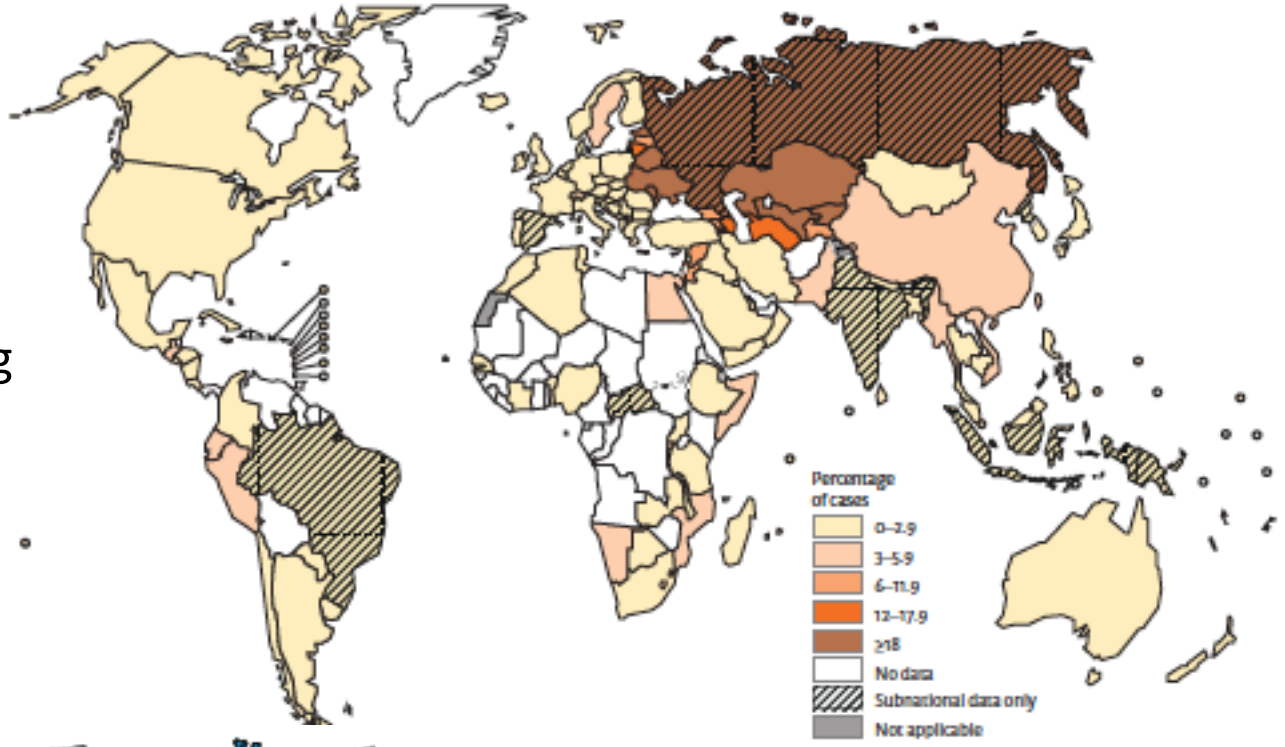
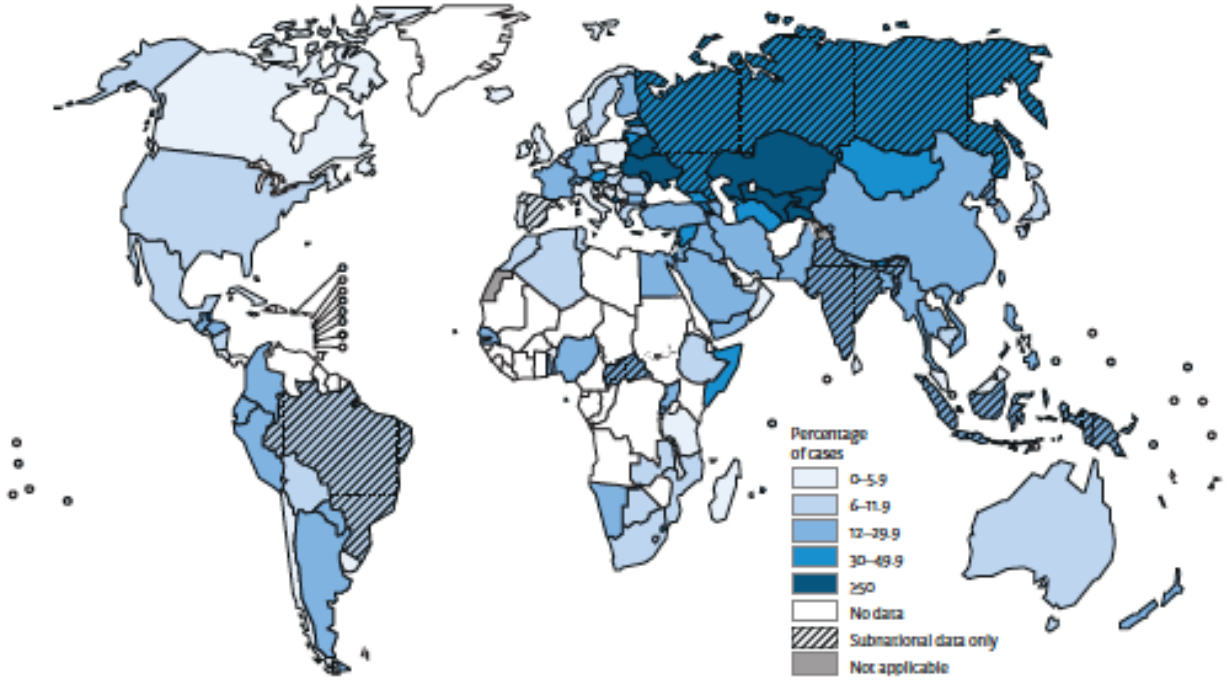
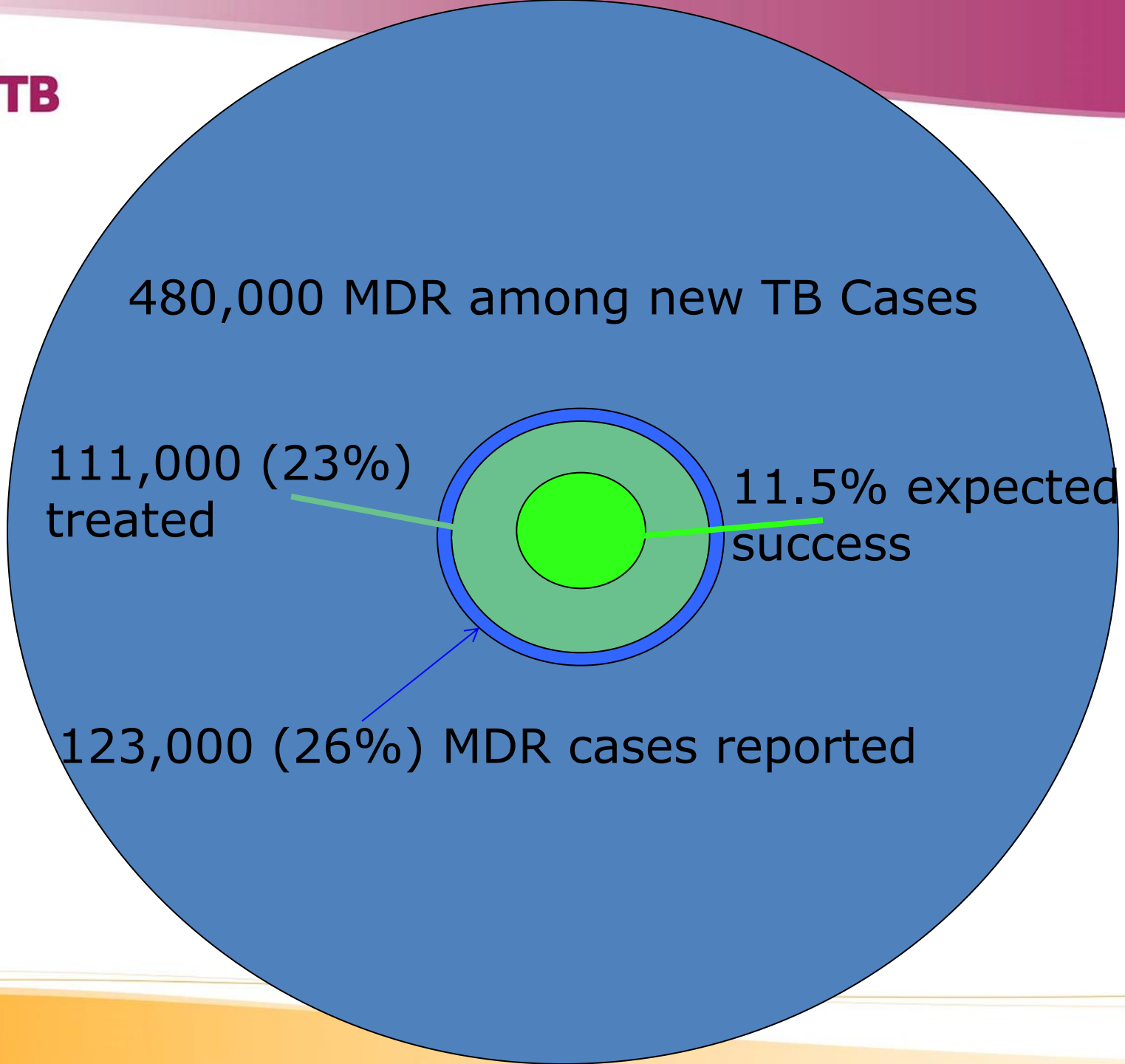
Co-PI endTB Clinical Trial

Prevalence of MDR-TB among new TB cases

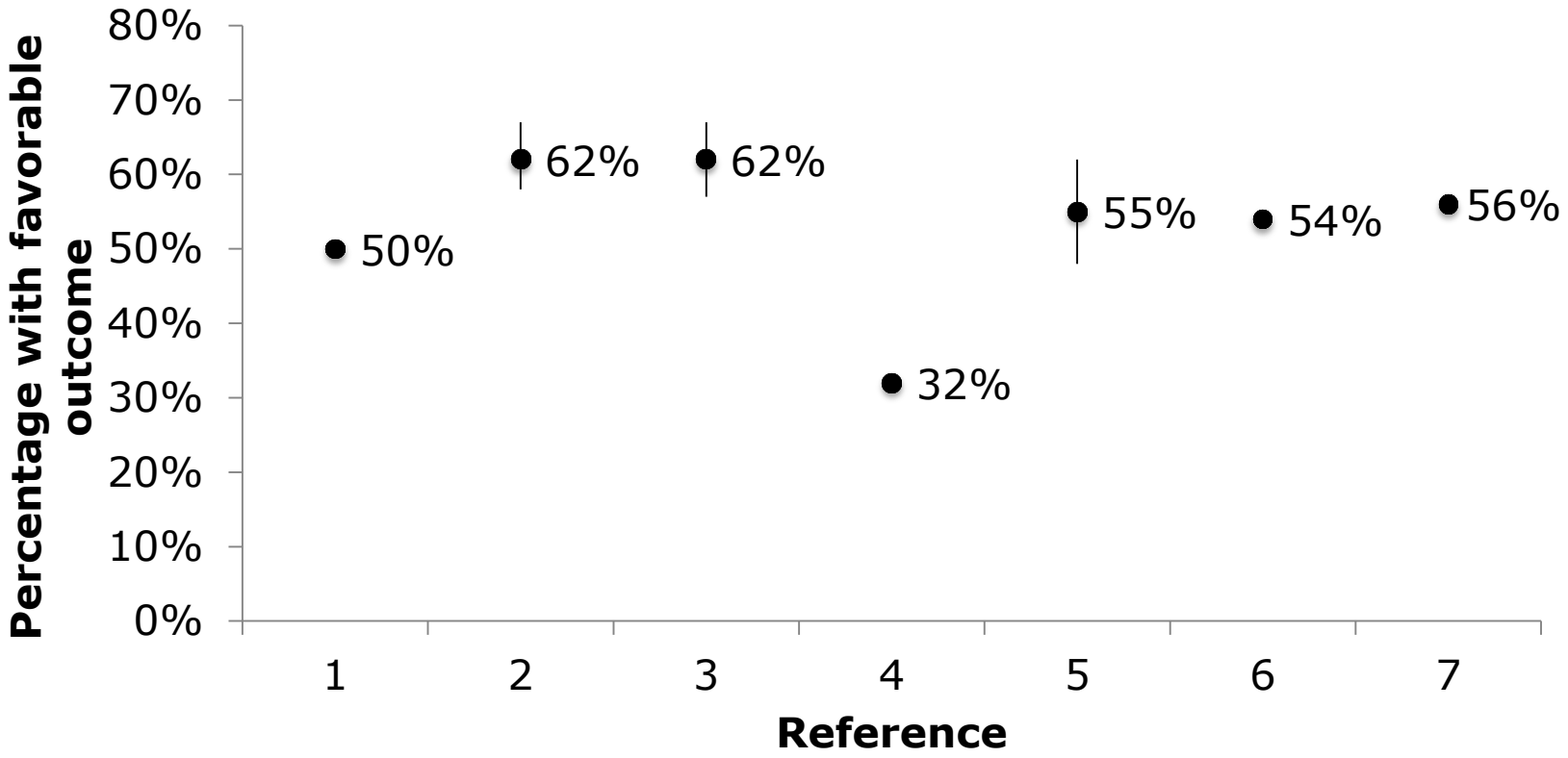



Prevalence of MDR-TB among previously treated TB cases

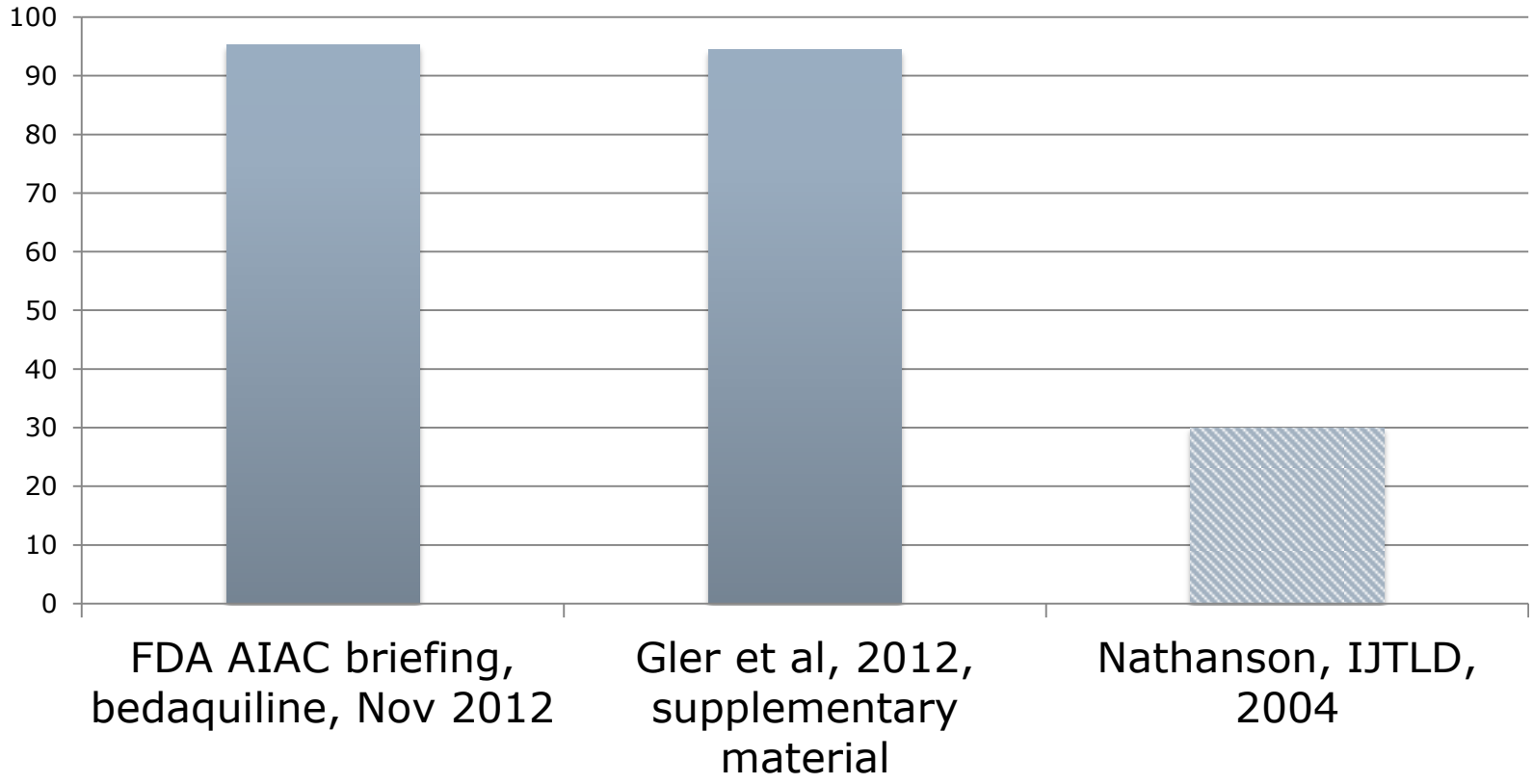

480,000 MDR among new TB Cases
111,000 (23%) treated
11.5% expected success
123,000 (26%) MDR cases reported

# Outcomes on existing MDR-TB treatment




[1]WHO Global Report, 2014; [2]Orenstein, Lancet, 2009*; [3]Johnston, PLoS, 2009*; [4]Diacon, NEJM, 2014; [5]Skriponoca, ERJ, 2013; [6]Ahuja, PLoS, 2012*; [7]Bonnet et al, IJTLD, 2016

# Frequency of adverse events (or AE indicating drug removal) on existing MDR-TB treatment



# Pill burden

Photo: Daily MDR-TB regimen in Mozambique. Why we're investing w/ @PIH, IRD & @MSF for better treatment! pic.twitter.com/j7zovDfIQ3 (UNITAID Twitter feed May 7, 2014)

**Typical Daily Pill Burden for MDR-TB/HIV Co-infected Patient >60 kg**

| Morning dose | Evening dose |
|---|---|
| Pyrazinamide: 4 tablets<br>Kanamycin: 1 g IM<br>Levofloxacin: 2 tablets<br>Ethionamide: 1 tablet<br>Cycloserine: 1 capsule<br>PAS: 1 sachet<br>AZT/3TC combination: 1 tablet<br>Cotrimoxazole: 1 tablet | Ethionamide: 2 tablets<br>Cycloserine: 2 capsules<br>PAS: 1 sachet<br>Pyridoxine: 4 tablets<br>AZT/3TC combination: 1 tablet<br>EFV (600 mg): 1 tablet |

# Cost of current MDR-TB treatment

| Regimen description | Drugs | Price Range for Regimens Using Quality-Assured Products |
|---|---|---|
| Standard Regimen for MDR-TB in Settings with No SLD Resistance | pyrazinamide, kanamycin, levofloxacin, ethionamide, cycloserine | USD $1,344 - $2,222 |
| Regimen for Patients with SLD Resistance | pyrazinamide, capreomycin, moxifloxacin, ethionamide, cycloserine, PAS | USD $5,267 - $7,339 |
| Regimen for XDR-TB or Failures of MDR-TB Treatment | capreomycin, moxifloxacin, cycloserine, clofazimine, linezolid, meropenem | USD $14,244 - $15,356 |

# Global TB Drug Pipeline [1]

**Discovery** | **Preclinical Development** | **Clinical Development**

**Lead Optimization** → **Early Stage Development** → **GLP Tox.** → **Phase I** → **Phase II** → **Phase III**

**Lead Optimization**

- Cyclopeptides
- Diarylquinolines
- DprE Inhibitors
- InhA Inhibitor, Indazoles
- LeuRS Inhibitors, Ureas
- Macrolides, Azaindoles
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Ruthenium(II) Complexes
- Spectinamides SPR-113
- Translocase-1 Inhibitors

**Early Stage Development**

- TBI-166
- CPZEN-45*
- SQ641*
- 1599*
- SEQ-9*

**GLP Tox.**

- PBTZ169*

**Phase I**

- TBA-354
- Q203*

**Phase II**

- Sutezolid (PNU-100480)
- SQ109*
- Rifapentine for DS-TB
- High Dose Rifampicin for DS-TB
- Bedaquiline-Pretomanid-Pyrazinamide Regimen
- Levofloxacin with OBR for MDR-TB

**Phase III**

- Bedaquiline (TMC-207) with OBR[2] for MDR-TB
- Delamanid (OPC-67683) with OBR for MDR-TB
- Pretomanid-Moxifloxacin-Pyrazinamide Regimen

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, , imidazopyridine amide, New chemical class*

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

[2] OBR = Optimized Background Regimen

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

| Title & Description | Status | Ph | Trial registry |
|---|---|---|---|
| 14-day EBA for dose optimization of AZD-5847 | Study completed; | 2 | NCT01516203 |
| BDQ combination in children and adolescents | To recruit in Russia & S. Africa | 2 | NCT02354014 |
| Safety & efficacy of BDQ for 24-48 weeks in MDR-TB; PK of BDQ & metabolite | Recruiting in Japan | 2 | NCT02365623 |
| STREAM I: 9-month Bangladesh regimen vs. SOC | Recruitment complete | 3 | ISRCTN78372190 |
| STREAM II: Comparison of 6- & 9-month BDQ regimens to SOC & Bangladesh (confirmatory) | Begin enrolling 2016: multisite | 3 | NCT02409290 |
| NEXT: 6-9 month all-oral regimen containing BDQ | Enrolling in S. Africa | 3 | NCT02454205 |
| Nix-TB: BDQ, pretomanid, and linezolid in patients with XDR-TB 6-9 months | Currently recruiting in S. Africa | 3 | NCT02333799 |
| GATB NC-005: Combinations of BDQ, MFX, PA-824, & PZA for 8 weeks for DS- & MDR-TB | Currently recruiting in Africa | 2 | NCT02193776 |
| STAND: MFX, PA-824, & PZA DS- & MDR-TB | Suspended | 3 | NCT02342886 |
| Linezolid and clarithromycin drug-interaction (PK) in MDR- & XDR-TB | Completed | 4 | NCT01521364 |
| DDI (PK) & combined QT effects of BDQ and DLM in MDR-TB | Expected to begin enrolling 2Q16 in S. Africa | 2 | NCT02583048 |
| Safety & efficacy study of DLM (Confirmatory) | Study completed | 3 | NCT01424670 |

# DRUG-RESISTANT TUBERCULOSIS CLINICAL TRIALS PROGRESS REPORT

RESIST-TB
Research Excellence to Stop TB Resistance

| Title & Description | Status | Ph | Trial registry |
|---|---|---|---|
| DLM PK in ped with MDR-TB | Enrollment complete > 6 years; pending <6 years | 2 | NCT01859923 |
| Dose-ranging ped study of DLM | Enrollment complete >6 years; pending < 6 years | 1 | NCT01856634 |
| Isoniazid dose-ranging EBA in DS- & INH-R TB | Currently recruiting in S. Africa | 2 | NCT01936831 |
| Opti-Q: dose-ranging LFX in FQ-S/MDR-TB | Recruiting in Peru & S. Africa | 2 | NCT01918397 |
| Molecular testing of PZA susceptibility to optimize MDR-TB treatment | Currently recruiting in China | 3 | NCT02120638 |
| Safety, tolerability, PK of TBA-354 in healthy adults | Ongoing, but not recruiting | 1 | NCT02288481 |
| TB-PRACTECAL: short, all-oral regimens containing BDQ & PA-824 in MDR- & XDR-TB | Enrollment in 2016 in Uzbekistan & Swaziland | 2/3 | NCT02589782 |
| PHOENIX: 6 months daily DLM vs. INH, prevention in MDR contacts | This study is in planning | 3 | Not yet registered |
| TB-CHAMP: 6 months daily LFX vs. placebo, prevention in ped MDR contacts | This study is in planning | 3 | Not yet registered |
| V-QUIN: 6 months daily LFX vs. placebo, prevention in MDR contacts | This study is in planning | 3 | Not yet registered |

# endTB summary: Regimen optimization

- Phase III randomized (adaptive), open-label trials
  - I: test 39-week regimens with 1 or 2 new drugs in patients with MDR, FQ-S
  - II: test regimens with 2 new drugs in patients with MDR, FQ-R

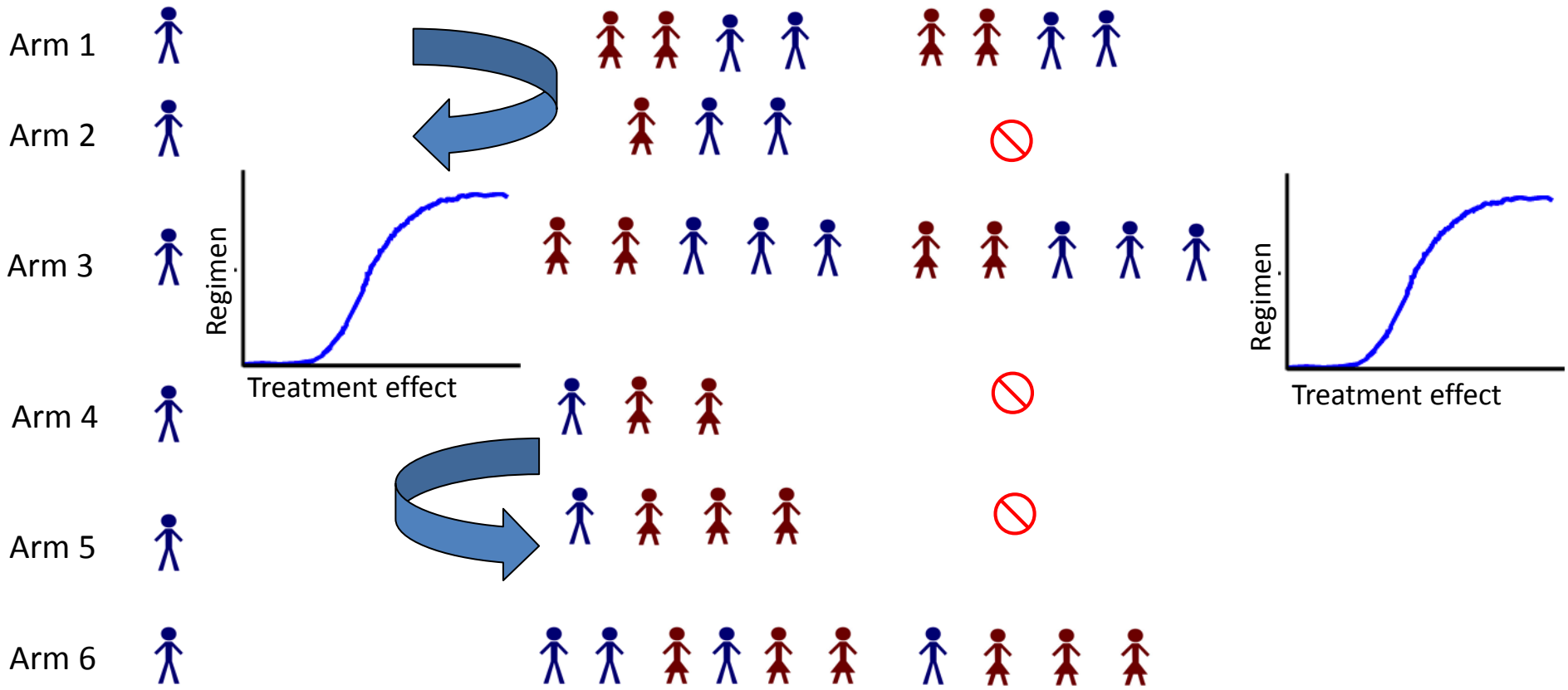
# endTB Trial Objectives

- **Efficacy**: assess efficacy at 8, 39, and 104 weeks
- **Safety/Tolerability:** assess frequency at 39 & 104 weeks of:
  1. treatment discontinuation due to toxicity;
  2. severe AEs (>=grade 3);
  3. SAEs;
  4. cardiac events;
  5. death.

# endTB Regimens (Stage I)

| Trial Regimens | Bedaquiline | Delamanid | Clofazimine | Linezolid | Fluoroquinolone | Pyrazinamide |
|---|---|---|---|---|---|---|
| **endTB 1 BeLiMoZ** | Be | | | Li | Mo | Z |
| **endTB 2 BeCLiLeZ** | Be | | C | Li | Le | Z |
| **endTB 3 BeDeLiLeZ** | Be | De | | Li | Le | Z |
| **endTB 4 DeCLiLeZ** | | De | C | Li | Le | Z |
| **endTB 5 DeCMoZ** | | De | C | | Mo | Z |
| **endTB 6 Control** | Standard of care, composed according to WHO Guidelines, including the possible use of De or Be. | | | | | |

Randomize to 6 arms → Observe & predict response-8 & 39 weeks → Adapt randomization → Drop inferior arms, end trial early, adjust sample size → Produce results



# Expansion of trial capacity: endTB trial sites